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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SPECTOR, L	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)
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EXAMINER	
ART UNIT	PAPER NUMBER
	7

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10/8/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-16 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-8, 10-16 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-16 are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

...OWING PAGES

Part III: Detailed Office Action

Formal Matters:

The claims as originally filed omitted claim number 6. Claims 7-17 have been renumbered under 37 C.F.R. § 1.126 as 6-16, respectively.

Restriction Requirement:

Applicant's election of Group I, claims 1-9 and 11-17 (renumbered 1-8 and 10-16) in Paper No. 6 filed 10/8/98 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 9 is withdrawn from consideration as being drawn to a non-elected invention.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 11-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for reciting "having agonist and/or antagonist activity". It is not clear *to what* the claimed protein has agonist and/or antagonist activity. It would appear that applicants contemplate that the claimed protein can be and agonist and antagonist of a single type of receptor, which is illogical. A similar objection applies to claims 11, 15 and 16.

Claim 3 is further indefinite the antecedent basis for "the receptor for the glycoprotein hormone" is not clear; claim 1, from which claim 3 depends, recites at least two separate

glycoprotein hormones.

Claim 4 is further indefinite for reciting "a position proximal to its C-terminus". Although preferred embodiments are set forth in the specification, limitations of the specification cannot be read into the claims. It is not clear from the claim itself what are the metes and bounds of "proximal".

Claim 4 is also indefinite as the metes and bounds of a "partial CTP unit" are not clear. Specifically, it is not clear what the minimum length of CTP sequence is within the metes and bounds of the claim. The definition at page 10 of the specification is noted, however, is in itself indefinite, containing conflicting references. For example, within the description therein, it would appear that a CTP unit must be at least 17 residues' long, representing the maximum 10 residues deletion allowed under the definition of "variant" from the minimum "full length" of 27 residues. However, the specification also states that the "partial CTP" preferably retains at least 1 O-linked glycosylation site. By the Examiner's calculation, there does not appear to be any fragment of the CTP unit of 17 residues' length which does not retain at least two of the O-linked glycosylation sites.

Claim 5 is indefinite for reciting "the α subunit or one or more β subunits or both". It is not clear whether "or both" refers to both the α and β subunits, or alternatively to both β subunits.

Claim 6 is indefinite as the metes and bounds of "truncated forms" are not clear. The specification provides inadequate guidance as to such, e.g. the minimum length and activity of such. Given that the claimed protein is a single chain trimer, not all of the subunits would have to retain any activity at all for the protein as a whole to have agonistic or antagonistic activity.

Claim 7 is indefinite as the metes and bounds of "suitable pharmaceutical excipient" cannot be determined in the absence of any intended use. Amendment to read "a pharmaceutically acceptable excipient" (or the like) would be remedial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for single chain proteins of the formula β^1-(linker^1)$_m$-α-(linker^2)$_n$-β^2 wherein α, β^1 and β^2 represent α and β subunits of LH, FSH, TSH and CG, does not reasonably provide enablement for the scope of subunits of any glycoprotein hormone, nor of the configurations β^1-(linker^1)$_m$-β^2-(linker^2)$_n$ - α, nor α -(linker^1)$_m$-β^1 -(linker^2)$_n$ β^2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents only a single working example, a protein having the structure CGβ-α-CTP-FSHβ. Enablement is not commensurate in scope with proteins of the formula β-β-α or α-β-β.

Enablement is not commensurate in scope with claims to any possible protein comprising a covalently linked glycoprotein hormone α and two β subunits. Several factors which limit the enabled scope of the invention include (a) the scope of the term "glycoprotein hormone", (b) the issue of non-recombinantly produced (i.e. non-fusion) proteins, (c) the issue of orientation of the two subunits (e.g. β^1-(linker^1)$_m$-β^2-(linker^2)$_n$ - α, nor α -(linker^1)$_m$-β^1 -(linker^2)$_n$ β^2 vs. β^1 -(linker^1)$_m$-α-(linker^2)$_n$-β^2), (d) the issue of linker moieties, (e) the issue of enablement of variant forms, including truncated forms, and (f) enablement of pharmaceutical compositions. Each of these will be discussed in turn:

(a) The scope of the term "glycoprotein hormone": The disclosure is enabling only for claims limited in scope to glycoprotein hormones selected from the group consisting of LH, FSH, CG and TSH. There exist other hormones, not within the scope of the instant disclosure, which may be glycosylated. The disclosure does not teach how to make or use other glycosylated hormones within the scope of the invention as it is claimed.

(b) The issue of non-recombinantly produced (i.e. non-fusion) proteins: The specification sets forth the invention as preferably being accomplished via recombinant DNA technology. However, the claims are not limited to such species, and the specification provides no teaching as to how to make the claimed proteins non-recombinantly, other than to state that "the α and β subunits as well

as the linkers may include amino acids that are not gene encoded"(page 5 lines 24-25), "the linkers may be other than peptide-such as dicarboxylic acids or anydrides, diamines, or bifunctional linkers..." (page 5 lines 26-27). Further, the specification states at page 10 that "the "linker moiety" may be one "which alters that activity (of the glycoprotein hormone) to convert it from agonist to antagonist activity". The sole working example in the specification uses the CTP as a linker moiety, and no guidance, other than that quoted above, is provided to allow the artisan to determine what linkers might be suitable in the context of the invention. The specification clearly is not enabling of such scope, especially as it pertains to linkers which alter the activity of the constituent glycoprotein hormone subunits, because it does not adequately describe the invention, it does not teach how to make the invention, and further, because is would require undue experimentation to determine which of the innumerable possible methods of covalently linking proteins would reasonably be expected to produce a protein which could be used as an agonist or antagonist as disclosed in the specification.

(c) The issue of orientation of the two subunits (e.g. β-α-β vs. β-β-α or α-β-β): The specification clearly indicates that the α and β subunits may be joined in any orientation. However, in the single working example, a single species is made recombinantly, consisting of CG β linked at its C terminus directly to the α subunit, which in turn is linked at its C terminus to a complete CTP unit, and then to an FSHβ subunit. This single working example was shown to bind to LH receptor in competition with hCG or FSH receptor in competition with FSH. It cannot be determined from the data in the specification as originally filed whether the observed binding is due to the ability of the α subunit to associate with each of the β subunits in the protein to form a domain which is capable of binding the appropriate receptor, or alternatively whether the subunits of the protein are actually associating with another single chain protein to form such structure, or alternatively whether the subunits do not associate at all but are capable of binding to receptor in "pseudo-monomeric" form. In the absence of any such information, as well as the absence of any other working examples, it is not predictable whether β-β-α or α-β-β forms will give similar results, nor whether and in what positions linkers would be necessary for the proteins to form the appropriate configurations for such binding. Further, the binding of the single exemplified species to receptor does not provide any

information as to whether that single species is an agonist or antagonist with respect to each of the two receptor types. Accordingly, enablement is not commensurate in scope with all the claimed orientations, and is further not enabling of agonist and antagonist activity of the claimed proteins.

(d) With respect to linker moieties, it is noted first of all that the linker sequence is not an inert "string", but would be expected to play a role in the folding and assembly of the protein. To set forth some simple examples, a linker might either unacceptably separate the subunits such that they would not assemble properly, or alternatively, depending on the sequence of the linker, might preferentially associate with one of the subunits preventing "normal" assembly of the pseudoheterodimer, or might result in preferential assembly of one of the β subunits with the α subunit to the exclusion of the other β subunit (presuming that intramolecular "assembly" is occurring at all). Factors that would affect the role of the linker would include the normal thermodynamics of the assembly process, the hydrophobic/hydrophilic properties of the linker sequence, the secondary structure of the linker (e.g. inclusion of pleated sheets or helices), and modifications of the linker, e.g. glycosylation, which can alter the flexibility of a peptide as well as its hydrophilicity. Further, as stated above, the specification suggests that the structure of the linker can be designed to modify the activity of the constituent subunits, but does not present any clarification of this suggestion, any suggestions as to possible linker structures for accomplishing such, nor any working examples of such linkers. In view of this, it is not predictable what types of sequences would be suitable for the linker, nor the functional range for length of such sequences would be (it is further noted that these factors would be expected to be different for each possible attachment site on each subunit, and each orientation of the two subunits). Although the level of skill in the art is high, and the ordinary artisan would be able to suggest possible linkers which would be expected to be "neutral" in effect, the specification essentially proposes various functions for the linker, and invites the artisan to experiment to determine operative species. In view of this, enablement is not commensurate in scope with claims to molecules comprising any type of linker.

This issue is further compounded in claims drawn to linker moieties which are themselves drugs. Although the specification at page 13 sets forth a limited number of envisioned species, it is

not clear what other types of drugs are envisioned as comprising the linker moiety, and further, it is unpredictable that a drug which was tethered at at least two points to glycoprotein hormone subunits would retain function. Such would depend upon the mechanism of action of the particular drug; for example, drugs often act by being internalized to the cell, where they specifically inhibit one or more processes. A drug that was trapped between the subunits of a hormone would not predictably be able to function in such fashion. It is unpredictable that such would be internalized, especially as the receptors for the disclosed glycoprotein hormones do not transport their ligands into the cell. Further, even *if* the drug were internalized, it is unpredictable that it would bind normally to its target molecules. Finally, the specification provides no guidance as to which drugs would be expected to be useful when coupled to which antagonistic molecules (and to what such molecules should be antagonistic), nor which agonistic molecules (and to what such molecules should be agonistic). It wold require undue experimentation to determine a commensurate number of species that (a) would be functional in the context of the single chain protein of the invention, and (b) for the treatment of what conditions such would be useful. Accordingly, the specification teaches neither how to make or use species which comprise such drugs.

(e) Enablement of variant forms, including truncated forms: It is noted that the specification discloses numerous publications in which variant forms of one or the other subunit of one of the hormones have been made and shown to be either agonists or antagonists of the naturally occurring sequences. Although the claims contain the functional limitation that the protein *as a whole* has agonist or antagonist activity, there is no requirement that each of the individual α and β subunits comprised in the protein have any activity at all. It would reasonably be expected that the number of non-functional variants of each individual subunit would vastly outnumber functional variants. However, the specification does not teach how to use proteins comprising species which have neither of those properties. In view of this, enablement is not commensurate in scope with claims to any and all possible types of variants or truncates.

With respect to insertion of CTP units within the α or β subunit sequence, although the specification gives limited information on essential regions of the α and β subunits, such is not

enabling of the scope of claims to insertions of complete or partial CTP units in non-critical regions of the proteins. Merely identifying a few critical residues does not imbue the reader with a reasonable expectation of success at making such insertions at any non-recited site, both because there may be additional critical regions, and because even "non-critical" regions may be critical to attaining the proper three-dimensional configuration of the protein.

(f) Enablement of pharmaceutical compositions: While the specification is reasonably enabling of pharmaceutical compositions comprising proteins which act as either agonists or antagonists of LH, CG, TSH or FSH, it does not teach how to use pharmaceutical compositions wherein the linker comprises a drug, for reasons cited above.

Given each of the factors discussed above, the presence of only a single working example, the fact that the prior art has not clearly elaborated the process by which the hormones are assembled, the unpredictably of each of the factors above, each of which is compounded by the others, and finally the breadth of the claims, the Examiner concludes that an undue amount of experimentation would be required to practice the invention in a manner commensurate with the scope of the claims.

Prior Art:

Thomason, U.S. Patent number 5,705,484 teaches a polypeptide in which "at least two monomeric polypeptide subunits of a naturally occurring multimeric protein are linked together as a single polypeptide ("fusion multimer")" (column 2, lines 55-59). The advantages of such are that they are more easily and rapidly refolded than unfused multimers, and the elimination of undesired by-products (col. 2 lines 60-67). At the top of column 3, Thomason states that the subunits may be directly linked or may be separated by a spacer moiety. Thomason envisions both biologically active fusion multimers, as well as fusion multimers that function as inhibitors of the native protein (col. 4, lines 21-30, col. 5 lines 62-63). Thomason's preferred species was PDGF, however the disclosure clearly contemplates any multimeric protein, see column 3 beginning at line 45. The exemplified host cell was *E. coli*, see Examples 5 and 6, column 16. Thomason does not teach or suggest making

higher order multimers of dimeric proteins.

Garvin et al. EP 0 163 406, teach a method for making desired peptides in quantity, involving the construction of cloning vehicles containing DNA which "codes for tandemly linked multiple copies of the polypeptide gene joined by linking sequences which code for easily-cleavable amino acid sequences." Garvin additionally teaches that "High yields of the multiple copy (polymeric) product are obtained and may be cleaved at the contrived joins to provide single polypeptides." (See abstract for both quotations; also see page 3 lines 13-17). Garvin discloses DNA constructs, vectors, transformed cells, and expression and isolation of the recombinantly produced product. At page 4, Garvin specifically teaches that the invention " has general applicability to the enhancement of stability of polypeptides in microorganisms and may be used to produce a wide variety of polypeptide products, comprising hormone polypeptides, including human and animal source polypeptides..." (see lines 5+). In the constructions exemplified by Garvin, the tandem iteration of the proinsulin sequence was preceded by a leader sequence which comprised the first 80 amino acids of the N-terminus of β-galactosidase (page 6, lines 1-5), which comprises a "signal sequence".

Gearing, U.S. Patent number 5,420,247, teaches the production of a polyvalent form of a protein, leukemia inhibitory factor receptor. The polyvalent form was synthesized recombinantly as a tandem iterations of a single polypeptide. At column 13, Gearing teaches that, for example, a bivalent form may consist of two tandem repeats separated by a linker sequence.

Reddy, WO 01959, is cited as teaching that nucleic acids encoding all four glycoprotein hormone beta subunits as well as the α subunit were available to the ordinary artisan at the time the invention was made.

La Polt et al., Endocrinology 131:2514, cited by applicants, disclose the attachment of the hCGβ carboxy terminal peptide (CTP) to FSHβ, resulting in increased *in vivo* potency and half-life of the protein (see abstract). At page 2514, first paragraph, La Polt et al. indicate that the effect is expected to have been due to the presence of O-linked oligosaccharides on the CTP. At page 2519, LaPolt et al. state that "In general, O-linked oligosaccharides confer increased stability to glycoproteins.

Boime, WO96/05224, cited by applicants, discloses fusion proteins comprising two β subunits of a hormone selected from the group consisting of FSH, TSH, LH, and CG. Boime does not teach or suggest fusion proteins comprising two β and one α subunit.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Lila Feisee, can be reached at (703)308-2731.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

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